SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished pharmaceutical product

INN Name: Darunavir and Ritonavir Tablets 800mg/100mg

Trade Name: Not Applicable

Strength: 800mg/100mg

Pharmaceutical form: Tablets

2. Qualitative and quantitative composition

Each Film coated tablets contains 867.28 mg of Darunavir Ethanolate equivalent to 800 mg of Darunavir and Ritonavir USP 100 mg.

3. Pharmaceutical form

Dosage form: Tablets

Description: Darunavir and Ritonavir Tablets 800/100 mg are Yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D24' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Darunavir and Ritonavir tablets is indicated in combination with other antiretroviral medicinal products for the treatment of with HIV-1 infection in antiretroviral therapy (ART)-naïve and treatment experienced adults and adolescents.

4.2 Posology and method of administration

Testing Prior to Initiation of Treatment

Fixed dose combination (FDC) of Darunavir 800 mg/600 mg/400 mg and Ritonavir 100 mg/100 mg/50 mg tablets will be administered orally once daily with food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.As this FDC is a fixed dose

combination of darunavir and ritonavir, contraindications to any of darunavir or ritonavir is applicable for this FDC.

Concomitant treatment with any of the following medicinal products given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect.

Applicable to darunavir boosted with either ritonavir or cobicistat:

- The combination product lopinavir/ritonavir.

Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance.

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin

- Patients with severe (Child-Pugh Class C) hepatic impairment.

Co-administration of darunavir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: dronedarone, amiodarone, bepridil, quinidine.
- Anti-gout: colchicine, in patients with renal/and or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide, quetiapine, sertindole
- Ergot derivatives, e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine

- GI motility agent: cisapride
- Herbal product: St. John's wort (Hypericum perforatum)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- HMG-CoA Reductase Inhibitors: lovastatin, simvastatin
- Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide
- Opioid Antagonist: naloxegol
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam
- Platelet aggregation inhibitor: ticagrelor, dabigatran
- Others; ivabradine, dapoxetine, domperidone, naloxegol, astemizole, terfenadine

Ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance.

- Anticancer Agents: apalutamide
- Herbal Products: St. John's Wort (hypericum perforatum)
- Ritonavir is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir or any of its ingredients. Co-administration of ritonavir with several classes of drugs (including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations) is contraindicated and may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of these drugs. Voriconazole and St. John's Wort are exceptions in that co-administration of ritonavir and voriconazole results in a significant decrease in plasma concentrations of voriconazole, and co-administration of ritonavir with St. John's Wort may result in decreased ritonavir plasma concentrations.

Drug Class	Drugs Within Class That Are Contraindicated With Darunavir/ritonavir	Clinical Comment
Alpha 1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Antianginal	Ranolazine	Potential for serious and/or life threatening reactions.
Antiarrhythmics	Amiodarone, dronedarone, flecainide, propafenone, quinidine, bepridil, encainide, quinidine	Potential for cardiac arrhythmias.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose-titration phase

Antifungal	Voriconazole	Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater due to the potential for loss of antifungal response.
Antigout	Colchicine	Potential for serious and/or life threatening reactions in patients with renal and/or hepatic impairment.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterial	Rifabutin	Concomitant use of ritonavir (500 mg twice daily) dosed as an antiretroviral agent and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse reactions including uveitis. Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted.
Antipsychotics	Lurasidone Pimozide Clozapine, Quetiapine	Potential for serious and/or life threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Analgesics	Pethidine, piroxicam, propoxyphne	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Ergot	Dihydroergotamine,	Potential for acute ergot toxicity characterized by

Derivatives	ergotamine, ergonovine, methylergonovine	vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to Ritonaviror to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
PDE5 enzyme inhibitor	Sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)	Potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope
	Avanafil	Increased plasma concentrations of avanafil
	Vardenafil	Increased plasma concentrations of vardenafil
Sedative/hypnotics	Oral midazolam, triazolam, Clorazepate, diazepam, estazolam, flurazepam,	Prolonged or increased sedation or respiratory depression
Microsomal triglyceride	Lomitapide	Increased plasma concentrations of lomitapide

transfer protein (MTTP) inhibitor		

4.4 Special warnings and precautions for use

As this FDC is a fixed dose combination of darunavir and ritonavir, warnings and precautions to any of darunavir or ritonavir is applicable for this FDC.

Darunavir and Ritonavir

Risk of Serious Adverse Reactions due to Drug Interactions

Initiation of darunavir/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving darunavir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of darunavir/ritonavir, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of darunavir/ritonavir.
- Loss of therapeutic effect of darunavir/ritonavir and possible development of resistance.

Diabetes Mellitus/Hyperglycemia

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV {direct acting antiviral / DAA} treatment. Glucose levels of diabetic patients initiating DAA therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor (PI) therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for

treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between PI therapy and these events have not been established. The physician in charge of the diabetic care of the patient should be informed when DAA therapy is initiated. Consider monitoring for hyperglycemia, new onset diabetes mellitus, or an exacerbation of diabetes mellitus in patients treated with ritonavir.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy (CART), including darunavir and ritonavir an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease, polymyositis, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable, and can occur many months after initiation of treatment.

Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Darunavir

Darunavir must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer darunavir with ritonavir and food may result in a loss of efficacy of darunavir.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with darunavir/ritonavir. During the clinical development program (N=3063), hepatitis was reported in 0.5% of patients receiving combination therapy with darunavir/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.

Post-marketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with darunavir/ritonavir therapy has not been established. Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on darunavir/ritonavir should prompt consideration of interruption or discontinuation of treatment.

Severe Skin Reactions

During the clinical development program (n=3063), severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, have been reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (less than 0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have been reported. Discontinue darunavir/ritonavir immediately if signs or symptoms of severe skin reactions develop.

These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with darunavir/ritonavir. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using darunavir/ritonavir was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir/ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Sulfa Allergy

Darunavir contains a sulfonamide moiety. Darunavir should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

Pediatric Patients

Do not administer darunavir/ritonavir in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age.

Ritonavir

Toxicity in Preterm Neonates

Ritonavir oral solution contains the excipients alcohol (43.2% v/v) and propylene glycol (26.57% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at an increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory

complications leading to death have been reported, predominantly in preterm neonates receiving lopinavir/ritonavir oral solution which also contains the excipients alcohol and propylene glycol. Ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. However, if the benefit of using ritonavir oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to ritonavir oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

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Hepatotoxicity

Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and

jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Increased AST/ALT monitoring should be considered in these patients, especially during the first three months of ritonavir treatment. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS.

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

Allergic Reactions/Hypersensitivity

Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.

PR Interval Prolongation

Ritonavir prolongs the PR interval in some patients. Post marketing cases of second or third degree atrioventricular block have been reported in patients.

Ritonavir should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR

interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended.

Lipid Disorders

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors.

Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

Laboratory Tests

Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating ritonavir therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Darunavir

Darunavir co-administered with ritonavir is an inhibitor of CYP3A, CYP2D6, and P-gp. Co-administration of darunavir and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6, or are transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events. Darunavir and ritonavir are metabolized by CYP3A. *In vitro* data indicate that darunavir may be a P-gp substrate. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of

darunavir and ritonavir and other drugs that inhibit CYP3A, or P-gp may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction	
Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**
HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Didanosine	↔ Darunavir ↔ Didanosine
Indinavir (The Reference Regimen For Indinavir Was Indinavir/Ritonavir 800/100 Mg Twice Daily.)	↑ Darunavir ↑ Indinavir
Lopinavir/ritonavir	↓ Darunavir ↔ Lopinavir
Saquinavir	↓Darunavir ↔ Saquinavir
HIV-1-Antiviral Agents: CCR5 co-receptor antagonists	
Maraviroc	↑ maraviroc
Other agents	
Alpha 1-adrenoreceptor antagonist: Alfuzosin	↑ alfuzosin
Antianginal: ranolazine	↑ ranolazine
Antiarrhythmics: Dronedarone **E.G.** Amiodarone, Bepridil, Disopyramide, Flecainide, Lidocaine (Systemic), Mexiletine, Propafenone,	↑ Dronedarone ↑ Antiarrhythmics

Quinidine, Digoxin, Dronedarone, Ivabradine, Ranolazine	↑ Digoxin
Antibacterial: clarithromycin	↔ Darunavir ↑ Clarithromycin
Anticoagulant: Apixaban Rivaroxaban Betrixaban Edoxaban Ticagrelor	 ↑ Apixaban ↑ Rivaroxaban ↔ Betrixaban ↔ Edoxaban
Other Anticoagulants Warfarin	↓ Warfarin ↔ Darunavir
Anticonvulsant: Carbamazepine	↔ Darunavir ↑ Carbamazepine
Clonazepam	↑ Clonazepam
Anticonvulsant: Phenobarbital, Phenytoin	↔ Darunavir ↓ Phenytoin ↓ Phenobarbital
Antidepressant: Selective Serotonin Reuptake Inhibitors (Ssris): Paroxetine, Sertraline Tricyclic Antidepressants (Tcas): Amitriptyline, Desipramine Imipramine, Nortriptyline Other: Trazodone	↓ Paroxetine ↓ Sertraline ↑ Amitriptyline ↑ Desipramine ↑ Imipramine ↑ Nortriptyline ↑ Trazodone
Antifungals: Itraconazole, Ketoconazole, Posaconazole	↑ Darunavir ↑ Itraconazole (Not Studied)

Voriconazole	↑ Ketoconazole ↔ Posaconazole (Not Studied) ↓ Voriconazole (Not Studied)
Anti-Gout: Colchicine	↑ Colchicine
Antimalarials: Artemether/Lumefantrine	↓ Artemether ↓ Dihydroartemisinin ↑ Lumefantrine ↔ Darunavir
Antimycobacterial: Rifabutin Rifabutin The Reference Regimen For Rifabutin Was 300 Mg Once Daily Rifapentine	↓ Darunavir ↓ Cobicistat ↑ Darunavir ↑ Rifabutin ↑ 25-*O* Desacetylrifabutin ↓ Darunavir
Antineoplastics: Dasatinib Nilotinib Vinblastine Vincristine, Irinotecan	↑Antineoplastics
Antipsychotics: Lurasidone Pimozide Quetiapine E.G. Perphenazine, Risperidone, Thioridazine	↑ Lurasidone ↑ Pimozide ↑ Quetiapine ↑ Antipsychotics
B-Blockers: E.G. Carvedilol, Metoprolol, Timolol	↑ Beta-Blockers
Calcium Channel Blockers: Amlodipine, Diltiazem, Felodipine,	↑ Calcium Channel Blockers

Nicardipine Nifedipine, Verapamil	
Ergot Derivatives: E.G. Dihydroergotamine, Ergotamine, Methylergonovine	↑ Ergot Derivatives
GI Motility Agent: Cisapride	↑ Cisapride
Lipid Modifying Agents: Hmg-Coa Reductase Inhibitors: Lovastatin, Simvastatin Atorvastatin, Pravastatin, Rosuvastatin Other Lipid Modifying Agents: Lomitapide	↑ Lovastatin ↑ Simvastatin ↑ Hmg-Coa Reductase Inhibitors ↑ Lomitapide
Corticosteroid (Systemic): Dexamethasone Corticosteroid (Systemic): Metabolized By CYP3A E.G. Budesonide**,** Prednisolone	↓ Darunavir ↑ Corticosteroide
Corticosteroid (Inhaled/Nasal): Budesonide, Fluticasone	↑ Corticosteroid
Endothelin Receptor Antagonists: Bosentan	↑ Bosentan
Hepatitis C Virus (HCV) Direct-Acting Agents: NS3-4A Protease Inhibitors: Boceprevir Telaprevir Simeprevir	↓ Darunavir ↓ Boceprevir ↓ Telaprevir ↑ Simeprevir ↑ Darunavir
Immunosuppressants: E.G. Cyclosporine, Tacrolimus, Sirolimus	↑ Immunosuppressants

Immunosuppressants/Neoplastic: Everolimus	
Inhaled Beta Agonist: Salmeterol	↑Salmeterol
Narcotic Analgesic/Treatment Of Opioid Dependence: Buprenorphine, Buprenorphine/Naloxone, Methadone	↔ Buprenorphine, Naloxone ↑ Norbuprenorphine (Metabolite) ↓ Methadone
Narcotic Analgesics Metabolized By CYP3A: E.G. Fentanyl, Oxycodone Tramadol	↑ Fentanyl ↑ Oxycodone ↑ Tramadol
Oral Contraceptives/Estrogen: Ethinyl Estradiol, Norethindrone Drospirenone	↓ Ethinyl Estradiol ↓ Norethindrone Drospirenone: Effects Unknown
PDE-5 Inhibitors: E.G. Avanafil, Sildenafil, Tadalafil, Vardenafil	↑ PDE-5 Inhibitors (Only The Use Of Sildenafil At Doses Used For Treatment Of Erectile Dysfunction Has Been Studied With Darunavir/Ritonavir)
Sedatives/Hypnotics: Orally Administered Midazolam, Triazolam **Metabolized By Cyp3a E.G.** Buspirone, Diazepam, Estazolam, Parenterally Administered Midazolam, Zoldipem	↑ Midazolam ↑ Triazolam ↑Sedatives/Hypnotics
Herbal Product: St. John's Wort (Hypericum Perforatum)	↓ Darunavir ↓ Cobicistat
Platelet Aggregation Inhibitor: Ticagrelor, Dabigatran	↑ Ticagrelor ↑ Dabigatran
Proton Pump Inhibitor:	↓ Omeprazole

Omeprazole	↔ Darunavir
Urological drugs: Fesoterodine Solifenacin	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary
Glecaprevir/pibrentasvir	↑ Glecaprevir and pibrentasvir
Domperidone	Not studied. Co-administration of domperidone with boosted darunavir is contraindicated.
Naloxegol	Co‑administration of boosted darunavir and naloxegol is contraindicated.
Dapoxetine	Co-administration of boosted darunavir with dapoxetine is contraindicated.

↑- Increase In Concentrations

↓- Decreased In Concentrations

↔ No Change In Concentrations

Ritonavir

Ritonavir has been found to be an inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with ritonavir. Thus, co-administration of ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.

Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

Established and Other Potentially Significant Drug Interactions.

Concomitant Drug Class: Drug Name	Effect on Concentration of Ritonavir or Concomitant Drug
HIV- Antiviral agents	
HIV-1 Protease Inhibitor: Atazanavir Darunavir Fosamprenavir	↑ Atazanavir ↑ Amprenavir ↑ Darunavir
HIV-1 Protease Inhibitor: Indinavir	↑ Indinavir
HIV-1 Protease Inhibitor: Saquinavir	↑ Saquinavir
HIV-1 Protease Inhibitor: Tipranavir	↑ Tipranavir
Non-Nucleoside Reverse Transcriptase Inhibitor: Delavirdine	↑ Ritonavir
HIV CCR5 – Antagonist: Maraviroc	↑ Maraviroc
Integrase Inhibitor: Raltegravir	↓ Raltegravir
Other agents	
Analgesics, Narcotic: tramadol, propoxyphene	↑ Analgesics ↓ Methadone ↑ Fentanyl
Anesthetic:	↓ meperidine /

meperidine	↑ normeperidine (metabolite)
Antialcoholics: disulfiram/ metronidazole	Ritonavir formulations contain ethanol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Antiarrhythmics: disopyramide, lidocaine, mexiletine	↑ Antiarrhythmics
Anticancer Agents: dasatinib, nilotinib, vincristine, vinblastine, neratinib, abemaciclib, apalutamide, encorafenib, venetoclax	↑ Anticancer Agents
Anticoagulant: warfarin	↓R-Warfarin ↓↑ S-Warfarin
Anticoagulant: rivaroxaban	↑ Rivaroxaban
Anticonvulsants: carbamazepine, clonazepam, ethosuximide	↑Anticonvulsants
Anticonvulsants: divalproex, lamotrigine, phenytoin	↓ Anticonvulsants
Antidepressants: nefazodone, selective serotonin reuptake inhibitors (SSRIs): e.g. fluoxetine, paroxetine, tricyclics: e.g. amitriptyline, nortriptyline	↑ Antidepressants
Antidepressant: bupropion	↓ Bupropion ↓ Active Metabolite, Hydroxybupropion
Antidepressant: desipramine	↑ Desipramine

Antidepressant: trazodone	↑ Trazodone
Antiemetic: dronabinol	↑ Dronabinol
Antifungal: ketoconazole itraconazole voriconazole	↑ Ketoconazole ↑ Itraconazole ↓ Voriconazole
Anti-gout: colchicine	↑ Colchicine
Anti-infective: clarithromycin	↑ clarithromycin
Antimycobacterial: Bedaquiline	↑ Bedaquiline
Antimycobacterial: Rifabutin	↑ Rifabutin And Rifabutin Metabolite
Antimycobacterial: Rifampin	↓ Ritonavir
Antiparasitic: Atovaquone	↓ Atovaquone
Antiparasitic: Quinine	↑ Quinine
β-Blockers: metoprolol, timolol	↑ Beta-Blockers
Bronchodilator: Theophylline	↓ Theophylline
Calcium Channel Blockers: Diltiazem, Nifedipine, Verapamil	↑ Calcium Channel Blockers

Digoxin	↑ Digoxin
Endothelin Receptor Antagonists: Bosentan	↑ Bosentan
HCV-Protease Inhibitor: Simeprevir	↑Simeprevir
HMG-Coa Reductase Inhibitor: Atorvastatin Rosuvastatin	↑ Atorvastatin ↑ Rosuvastatin
Immunosuppressants: Cyclosporine, Tacrolimus, Sirolimus (Rapamycin)	↑ Immunosuppressants
Steroids: Dexamethasone, Fluticasone, Prednisone Inhaled Or Intranasal Steroid: E.G. Fluticasone Budesonide	↑ Glucocorticoids
Long-Acting Beta- Adrenoceptor Agonist: Salmeterol	↑ Salmeterol
Narcotic Analgesic: Methadone Fentanyl	↓ Methadone ↑ Fentanyl
Neuroleptics: Perphenazine, Risperidone,	↑ Neuroleptics

Thioridazine	
Oral Contraceptives Or Patch Contraceptives: Ethinyl Estradiol	↓ Ethinyl Estradiol
Pde5 Inhibitors: Avanafil Sildenafil, Tadalafil, Vardenafil	↑ Avanafil ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil
Sedative/Hypnotics: Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem	↑ Sedative/Hypnotics
Sedative/Hypnotics: Parenteral Midazolam	↑ Midazolam
Stimulant: Methamphetamine	↑ Methamphetamine
Ibrutinib	↑ Ibrutinib Concentration.
Thyroid hormone replacement therapy Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.
Lipid-modifying agents Lomitapide	↑ Lomitapide

HCV Direct Acting Antiviral Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Vitamin K antagonists	leading to a reduced international normalized ratio (INR)
Lopinavir/ritonavir, along with quetiapine	Major sedation due to drug interaction between lopinavir/ritonavir and quetiapine
Levothyroxine	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism

4.6 Fertility, pregnancy and lactation

Pregnancy

Darunavir and ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No adequate and well-controlled studies of darunavir and ritonavir have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice and rats in the presence or absence of ritonavir as well as in rabbits with darunavir alone. In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir and ritonavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for

serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving darunavir and ritonavir.

Pediatric Use

Darunavir/ritonavir should not be administered in pediatric patients below 3 years of age because of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age.

The safety, pharmacokinetic profile, and virologic and immunologic responses of darunavir/ritonavir were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighting at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults.

In clinical trial, the safety, pharmacokinetic profile and virologic and immunologic responses of darunavir/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects). Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a darunavir/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted darunavir exposures for the dosing recommendations in this age group.

In HIV-infected patients age greater than 1 month to 21 years, the antiviral activity and adverse event profile of ritonavir seen during clinical trials and through postmarketing experience were similar to that for adult patients.

Geriatric Use

Clinical studies of darunavir/ritonavir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should

be exercised in the administration and monitoring of darunavir/ritonavir in elderly patients, reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy.

Hepatic impairment

No dose adjustment of darunavir/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of darunavir/ritonavir in subjects with severe hepatic impairment. Therefore, darunavir/ritonavir is not recommended for use in patients with severe hepatic impairment.

Renal Impairment

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). No pharmacokinetic data are available in HIV-1infected patients with severe renal impairment or end stage renal disease; however, because the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

Effects on ability to drive and use machines

Darunavir in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing darunavir co-administered with cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

Adverse reactions are listed by system organ class (SOC) and frequency category. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon

(≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing

MedDRA system organ class **Frequency category**	**Adverse reaction**
Infections and infestations	
Uncommon	Herpes simplex
Blood and lymphatic system disorders	
Uncommon	Thrombocytopenia, neutropenia, anaemia, leukopenia
Rare	Increased eosinophil count
Immune system disorders	
Uncommon	Immune reconstitution inflammatory syndrome, (drug) hypersensitivity
Endocrine disorders	
Uncommon	Hypothyroidism, increased blood thyroid stimulating hormone
Metabolism and nutrition disorders	
Common	Diabetes mellitus, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia
Uncommon	Gout, anorexia, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase

Psychiatric disorders	
Common	Insomnia
Uncommon	Depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido
Rare	Confusional state, altered mood, restlessness
Nervous system disorders	
Common	Headache, peripheral neuropathy, dizziness
Uncommon	Lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence
Rare	Syncope, convulsion, ageusia, sleep phase rhythm disturbance
Eye disorders	
Uncommon	Conjunctival hyperaemia, dry eye
Rare	Visual disturbance
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, prolonged electrocardiogram qt, tachycardia
Rare	Acute myocardial infarction, sinus bradycardia, palpitations
Vascular disorders	
Uncommon	Hypertension, flushing

Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, epistaxis, throat irritation
Rare	Rhinorrhoea
Gastrointestinal disorders	
Very common	Diarrhoea
Common	Vomiting, nausea, abdominal pain, increased blood amylase, dyspepsia, abdominal distension, flatulence
Uncommon	Pancreatitis, gastritis, gastrooesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia
Rare	Stomatitis, haematemesis, cheilitis, dry lip, coated tongue
Hepatobiliary disorders	
Common	Increased alanine aminotransferase
Uncommon	Hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	
Common	Rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus
Uncommon	Angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne,

	dry skin, nail pigmentation
Rare	Dress, stevens-johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma
Not known	Toxic epidermal necrolysis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia, osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphokinase
Rare	Musculoskeletal stiffness, arthritis, joint stiffness
Renal and urinary disorders	
Uncommon	Acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria
Rare	Decreased creatinine renal clearance
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, gynaecomastia
General disorders and administration site conditions	
Common	Asthenia, fatigue
Uncommon	Pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain
Rare	Chills, abnormal feeling, xerosis

Adverse reactions with darunavir/cobicistat in adult patients

MedDRA system organ class Frequency category	Adverse reaction
Immune system disorders	
Common	(Drug) Hypersensitivity
Uncommon	Immune Reconstitution Inflammatory Syndrome
Metabolism and nutrition disorders	
Common	Anorexia, Diabetes Mellitus, Hypercholesterolaemia, Hypertriglyceridaemia, Hyperlipidaemia
Psychiatric Disorders	
Common	Abnormal Dreams
Nervous System Disorders	
Very Common	Headache
Gastrointestinal Disorders	
Very Common	Diarrhoea, Nausea
Common	Vomiting, Abdominal Pain, Abdominal Distension, Dyspepsia, Flatulence, Pancreatic Enzymes Increased
Uncommon	Pancreatitis Acute
Hepatobiliary disorders	
Common	Hepatic Enzyme Increased
Uncommon	Hepatitis*, Cytolytic Hepatitis*

Skin And Subcutaneous Tissue Disorders	
Very Common	Rash (Including Macular, Maculopapular, Papular, Erythematous, Pruritic Rash, Generalised Rash, And Allergic Dermatitis)
Common	Angioedema, Pruritus, Urticaria
Rare	Drug Reaction With Eosinophilia And Systemic Symptoms*, Stevens-Johnson Syndrome*
Not Known	Toxic Epidermal Necrolysis*, Acute Generalised Exanthematous Pustulosis*
Musculoskeletal And Connective Tissue Disorders	
Common	Myalgia
Uncommon	Osteonecrosis*
Reproductive System And Breast Disorders	
Uncommon	Gynaecomastia*
General Disorders And Administration Site Conditions	
Common	Fatigue
Uncommon	Asthenia
Investigations	
common	increased blood creatinine

* These adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

Ritonavir

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia) and fatigue/asthenia.

The following adverse reactions of moderate to severe intensity with possible or probable relationship to ritonavir have been reported. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1000 to < 1/100); rare (> 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Events noted as having frequency not known were identified via post-marketing surveillance.

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity including urticaria, and face oedema
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually

		associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance, vomiting, dyspepsia
	Common	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue	Very common	Pruritus, rash (including erythematous and

disorders		maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculosketal and connective tissue disorders	Very common	Arthralgia and back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g. oliguria, elevated creatinine)
	Uncommon	Acute renal failure
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common	Increased amylase, decreased free and total thyroxin
	Uncommon	Increased glucose, increased magnesium, increased alkaline phosphatase

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs.

4.9 Overdose

Human experience of acute overdose with darunavir/ritonavir is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

No specific antidote is available for overdose with darunavir and ritonavir. Treatment of overdose with darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors

ATC code: J05AE10.

Mechanism of action:

Darunavir

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC50 values ranging from less than 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the PIs amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, rilpivirine, efavirenz, etravirine, or nevirapine, and the fusion inhibitor enfuvirtide.

Ritonavir

Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to production of non-infectious immature HIV particles. The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC50) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate

and the cells employed. The average EC50 value for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

5.2 Pharmacokinetics properties

Darunavir

Antiviral activity *in vitro*

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/ml). Darunavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM.

These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 μM to > 100 μM.

Resistance

In vitro selection of darunavir-resistant virus from wild type HIV-1 was lengthy (> 3 years). The selected viruses were unable to grow in the presence of darunavir concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to darunavir (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the protease gene. The decreased susceptibility

to darunavir of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations.

Ritonavir

Ritonavir dosed as a pharmacokinetic enhancer

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor. For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism.

Ritonavir dosed as an antiretroviral agent

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. However, due to ritonavir's metabolic inhibitory properties its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice.

Effects on the Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) difference in QTcF from placebo was 5.5 (7.6) for 400 mg twice daily ritonavir. The Day 3 ritonavir exposure was approximately 1.5 fold higher than that observed with the 600 mg twice daily dose at steady state. No subject experienced an increase in

QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11.0 to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed.

Resistance

Ritonavir-resistant isolates of HIV-1 have been selected *in vitro* and isolated from patients treated with therapeutic doses of ritonavir.

Reduction in the antiretroviral activity of ritonavir is primarily associated with the protease mutations V82A/F/T/S and I84V. Accumulation of other mutations in the protease gene (including at positions 20, 33, 36, 46, 54, 71, and 90) can also contribute to ritonavir resistance. In general, as mutations associated with ritonavir resistance accumulate, susceptibility to select other PIs may decrease due to cross-resistance.

Pharmacokinetic properties

Absorption

Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T_{max} of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively. In vivo data suggest that darunavir/ritonavir is an inhibitor of the p-glycoprotein (p-gp) transporters.

The absolute bioavailability of ritonavir has not been determined. After a 600 mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting (514 KCal; 9% fat, 12% protein, and 79% carbohydrate) conditions, respectively. Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, $AUC_{(0-\infty)}$ met equivalence criteria but mean C_{max} was increased by 26% (92.8% confidence intervals: ↑15 -↑39%). No

information is available comparing ritonavir tablets to ritonavir capsules under fasting conditions.

Distribution

Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

The apparent volume of distribution (VB/F) of ritonavir is approximately 20 - 40 l after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99% and is constant over the concentration range of 1.0 – 100 μg/ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV-1.

Nearly all of the plasma radioactivity after a single oral 600 mg dose of ^{14}C-ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. *In vitro* studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M–2.

Elimination

A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged

darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when co-administered with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

In a study of five subjects receiving a 600 mg dose of ^{14}C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

Ritonavir Pharmacokinetic Characteristics

Parameter	N	Values (Mean ± SD)
Vβ/F‡	91	0.41 ± 0.25 L/kg
t½		3 - 5 h
CL/F SS†	10	8.8 ± 3.2 L/h
CL/F‡	91	4.6 ± 1.6 L/h
CLR	62	< 0.1 L/h
RBC/Plasma Ratio		0.14
Percent Bound*		98 to 99%

†SS = steady state; patients taking ritonavir 600 mg q12h.

‡Single ritonavir 600 mg dose.

* Primarily bound to human serum albumin and alpha-1 acid glycoprotein over the ritonavir concentration range of 0.01 to 30 µg/mL.

5.3 Preclinical safety data

Animal Toxicology or Pharmacology

Darunavir:

Animal toxicology studies have been conducted at exposures up to clinical exposure levels with darunavir alone, in mice, rats and dogs and in combination with ritonavir in rats and dogs.

In repeated-dose toxicology studies in mice, rats and dogs, there were only limited effects of treatment with darunavir. In rodents the target organs identified were the haematopoietic system, the blood coagulation system, liver and thyroid. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated partial thromboplastin time.

Changes were observed in liver (hepatocyte hypertrophy, vacuolation, increased liver enzymes) and thyroid (follicular hypertrophy). In the rat, the combination of darunavir with ritonavir lead to a small increase in effect on RBC parameters, liver and thyroid and increased incidence of islet fibrosis in the pancreas (in male rats only) compared to treatment with darunavir alone. In the dog, no major toxicity findings or target organs were identified up to exposures equivalent to clinical exposure at the recommended dose.

In a study conducted in rats, the number of corpora lutea and implantations were decreased in the presence of maternal toxicity. Otherwise, there were no effects on mating or fertility with darunavir treatment up to 1,000 mg/kg/day and exposure levels below (AUC-0.5 fold) of that in human at the clinically recommended dose. Up to same dose levels, there was no teratogenicity with darunavir in rats and rabbits when treated alone nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, darunavir with and without ritonavir, caused a transient reduction in body weight gain of the offspring pre-weaning and there was a slight delay in the opening of eyes and ears. Darunavir in combination with ritonavir caused a reduction in the number of pups that exhibited the startle response on day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post weaning functions were affected with darunavir alone or in combination with ritonavir. In juvenile rats receiving darunavir up to days 23-26, increased mortality was observed with convulsions in some animals. Exposure in plasma, liver and brain was considerably higher than in adult rats after comparable doses in mg/kg between days 5 and 11 of

age. After day 23 of life, the exposure was comparable to that in adult rats. The increased exposure was likely at least partly due to immaturity of the drug-metabolising enzymes in juvenile animals. No treatment related mortalities were noted in juvenile rats dosed at 1,000 mg/kg darunavir (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats.

Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, darunavir with low dose ritonavir should not be used in paediatric patients below 3 years of age.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1,000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular and thyroid tumours in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to darunavir were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses.

After 2 years administration of darunavir at exposures at or below the human exposure, kidney changes were observed in mice (nephrosis) and rats (chronic progressive nephropathy).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

Ritonavir:

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and

were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

Ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Long term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.

6. Pharmaceutical particulars

6.1 List of excipients

Crospovidone, Hypromellose 5 cps, Silicified microcrystalline cellulose, Copovidone, Colloidal Silicon Dioxide, Magnesium stearate, Sorbitan monolaurate, Dibasic Calcium phosphate anhydrous, Dibasic calcium phosphate dihydrate, Microcrystalline cellulose, Corn starch, Mannitol, Sodium stearyl Fumarate, Purified water, Opadry yellow 16C82767.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30˚C and protect from moisture

6.5 Nature and contents of container

60's and 180's HDPE container

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1 Marketing Authorisation Holder

Name	:	**M/s. Hetero Labs Limited,**
Business Address	:	7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018 Telangana, INDIA
Telephone	:	+91-040-23704923/24/25
Fax	:	+91-40-23704035/23813359

7.2 Name and Address of Manufacturer

Manufacturing Site:

Name:	**Hetero Labs Limited Unit-III,**
Business Address:	HETERO LABS LIMITED, Unit-III 22-110, IDA, Jeedimetla, Hyderabad-500055 Telangana, India.
Country:	INDIA
Phone:	91-1795-247301/245732,

8. Registration Number

Not Applicable

9. Category for Distribution

Prescription only medicine – List I

10. Date of revision of the text